UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,532	12/11/2001	Julio C. Medina	11134-005-999	4305

20583 7590 10/09/2003

PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 100362711

EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	16

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,532	MEDINA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-159,162-170,173-190,193-197 and 202-204* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136-139,142,143,145,147,149,153-158,162-170,173-190,193-197 and 202* is/are rejected.

7)☒ Claim(s) *140,141,144,146,148,150-152,202 and 203* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 9/15/03. Applicant has amended claims 136 and 173. Applicants have canceled claims 160, 161, 171, 172, 191, 192, and 198-202. . There are forty-nine claims pending and forty-nine under consideration. Claims 136-152 are compound claims. Claim 153 is a composition claim. Claims 154-159, 162-170, 173-190, 193-197, and 202-204 are use claims. This is the second action on the merits. The application concerns some pyrido[2,3-d]pyrimidine compounds, compositions, and uses thereof.

Response to Amendment

2. Applicants' cancellation of the affected claims renders moot the objection made in point #4 of the previous office action. Applicants deletion of X = a bond from the claimed subject matter overcomes the objection made in point #5. Applicants' amendments overcome the formal objections made in points #6 and #7. Applicants no longer claim priority to Provisional Application 60/255,241. Thus, the denial of priority made in point #8 is moot. Claim 161 is no longer pending. Thus, the objection made in point #10 is moot. As Applicants correctly noted, claim 161 had been withdrawn from consideration, in any case, in the previous office action.

Applicants' have withdrawn claims to "prodrugs". Thus, the indefiniteness rejection made in point #12 and the enablement rejections in points #15 and #16

are overcome. Applicants' correction of an erroneous claim dependency overcomes the indefiniteness rejection made in point #13. Applicants point to claims 203 and 204, correctly asserting that these two claims do not contain any limitations drawn to disease treatment. Thus, then enablement rejection to claims 203 and 204, made in point #17 is withdrawn. The obviousness rejections made to claims 203 and 204, made in points #18 and #19 are withdrawn for the same reasons. Neither piece of prior art used in making these rejections teaches CXCR3 function.

Applicants assert that claims 51, 66, 79, 97, and 110 of copending Application No. 10/164,690 were canceled by preliminary amendment. The file is unavailable to the Examiner. However, based on Applicants' assertion and assuming the overlapping claims were not replaced by ones of similar scope, the double patenting rejection made in point #20 is withdrawn. Applicants have requested clarification of the indication of allowable subject matter made in point #21. Applicant's compounds are patentable over WO 01/16114 A (ref AT), not WO 01/16144 as previously stated. This reference does not teach the pyrido[2,3-d]pyrimidine core of the present claims.

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional applications upon which priority is

claimed remains to lack adequate support under 35 U.S.C. 112 for claims 136-159, 162-179, 174-190, 193-197, and 202-204 of this application. Provisional Application 60/296,499 differs in several ways from the presently claimed subject matter. The broadest teaching in 60/296, 499 is formula (I) on page 12. The variable Y^4 in figure corresponds to the N-R^{14} of the present claims. In the definition of R^{14} in 60/296, 499, both heteroaryl and aryl are mentioned. The present claims included substituted heteroaryl and substituted aryl groups. The substituted aryl and heteroaryl groups lack any support in the provisional application.

Formula (I) in 60/296, 499 is a monocyclic structure. The present claims are drawn to bicyclic compounds. In 60/296, 499 we are taught that Y^1 and Y^2 can form a six-membered heteroaryl ring. Nowhere is the nature of this ring stated. Nowhere is the presently claimed 2,3-fused pyridine indicated as a general possibility. The figures on page 14 of Provisional Application 60/296, 499 include the presently claimed 4-one compounds but exclude the presently claimed 4-dihydro compounds. In addition, formulas II and III, page 17 of Provisional Application 60/296, 499 are drawn to bicyclic compounds as is the present Application. However, the R^{14} variable of each formula is restricted to five

specific fused aromatic rings, not the present open-ended claim to aryl and heteroaryl.

Applicants argue that their present claims are fully supported by Provisional Application 60/296,499 and point to the formula III on page 17 of the provisional application. The present definitions of variables A^4, X, R^1, R^2, Q, L, n, and R_a have support in the corresponding definition for figure III in the provisional application. The present definitions of variables R^3, R^4, R^9, R^{10}, and R^{11} have support in the corresponding definitions for figure I, beginning on page 12 of the provisional application. However, as explained above the present R^{14} has no support in either place and is broader than taught in Provisional Application 60/296,499.

Claim Objections

4. Objection remains to claims 156, 157, 170, and 190 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In lines 2-8, page 13, 9-14, page 18, and 2-4, page 19 Applicants state that all compounds of the formula of claim 136 are antagonists of CXCR3. Thus, there are no compounds of claim 136 excluded in these four claims. In the alternative, if Applicants are aware of any compounds of the

claimed formula that are not antagonists of this chemokine, then please inform the Examiner so that the proper utility rejection may be made.

Applicants argue that testing procedures to determine the biological properties of their compounds are provided in the specification. They further argue that some inoperative embodiments are allowed. Applicants state that these objected claims are drawn only to disclaiming these inoperative embodiments. Both of these assertions are true but unfortunately, these assertions are at odds with what their specification says. The passage cited above states that all compounds, not most of them or even some of them are CXCR3 antagonists. Are Applicants now admitting that it is possible that only a few of their claimed compounds are CXCR3 antagonists?

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 187, 190, and 202 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a CXCR3-mediated condition or disease". It is unclear what diseases and treatments applicant is intending to encompass. Applicants define the phrase in lines 3-20, page 25 but repeatedly indulge in

speculation, "might" "may be". Are the diseases listed in lines 3-20 CXCR3 related or not? The passage spanning line 26, page 25 to line 30, page 26 lists a number of disease conditions without clarifying if these diseases are related to CXCR3. Are all infections, for example CXCR3-related diseases? Determining whether a given disease responds or does not respond to such a chemokine antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Applicants argue that the physician who must understand the meaning of this phrase could perform an assay for CXCR3 receptors to determine if any disease or any particular patient is suffering from "a CXCR3-mediated condition or disease". In answer to the Examiners question about infections, they admit that some infections are so related and some are not. They also point to Agostini (Exhibit 1) and Sorensen (Exhibit 2) as publications to define the phrase. These are not convincing. Firstly, as discussed below, no physician performs a CXCR3 receptor assay as part of routine clinical practice today. It is unclear that in 2001, Applicants effective filing date, there was even a single physician in the US trained

to perform such an assay. In any event, such an assay would be unable to distinguish between diseases which were the result of malfunctioning CXCR3 receptors and which diseases caused a malfunction to CXCR3 receptors.

Secondly, Applicants state that not all infections caused by the same organism are "a CXCR3-mediated condition or disease". This is apparently a complex phenomenon and depends upon the individual patient. The Applicants seem to be making the Examiner's point for him. If only some but not all TB patients, say, suffer from "a CXCR3-mediated condition or disease", then how is the average physician to understand the meaning of the term. Thirdly, neither reference cited by Applicants uses the phrase "a CXCR3-mediated condition or disease". Where in either reference is the list of diseases, which define this term?

Suppose that a given drug, which has receptor antagonist properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given

drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related receptor antagonists must be tried before one concludes that a specific disease does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are receptor antagonists *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example, agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

F. Even the most desired outcome does not unequivocally establish the meaning of the phrase. Our drug alone could be an effective treatment of the disease of interest. One still cannot conclude that the disease cured is "a CXCR3-

mediated condition or disease". What if our drug has a second biological effect in addition to CXCR3 receptor antagonism? It is possible that this second mechanism is responsible for the positive outcome.

Consequently, determining the true scope of the claim will require potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claims are indefinite.

6. Claims 154-159, 162-170, 173-190, 193-197, and 202 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would treat any particular human disease would require synthesis of the compound, formulation

into a suitable dosage form, and either subjecting it clinical trials with a number of fundamentally different diseases described below or subjecting it to testing in an art-recognized disease model, which is correlated to clinical efficacy. Considering the huge number of compounds embraced by claim 154 and the apparently limitless and unknown list of diseases to be tested, this would require a huge degree of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 30, page 24 to line 30, page 26, which merely states Applicants' intention to do so. Applicants describe formulations in line 29, page 21 to line 23, page 24. There are no working examples of any formulation required for the clinical practice of Applicants' invention. Possible routes of administration are taught in lines 31, page 26 to line 3, page 27. Possible doses and dosing schedules required to practice their invention are taught in lines 4 to 22, page 27. A 10,000-fold range of dosage is contemplated. Since no CXCR3 antagonist has ever been used to treat any human disease, how the skilled physician to know what dose to administer to her patients? There is a single *in vitro* assay described in the passage spanning line 14, page 162 to line 14, page 163 with no data. Applicants have not asserted and it is not art-recognized that the results of this *in vitro* assay are correlated to clinical efficacy of any disease treatment. There is no art-recognized *in vivo* disease models used to test Applicants' compounds.

c) There is no working example of treatment of any disease in man or animals. There are no working examples of the formulations, doses, and dosing schedules required by the physician to practice Applicants' invention. d) The nature of the invention is clinical treatment of disease with antagonists of the CXCR3 receptor, which involves physiological activity. e) The state of the clinical arts with CXCR3 antagonists is provided by Carter (Curr. Opin. Chem. Biol.) who reports in Table 1, page 512, that mice lacking CXCR3 receptors are normal. In the paragraph spanning pages 513-514 elevated levels of this chemokine are reported in both psoriasis and MS patients, although no treatment of any such patients by antagonists of this chemokine were known in 2002. Table 3, page 516 makes clear that no CXCR3 antagonists were known in 2002. Thus, logically no diseases treatable by such antagonists could have been found by this date.

Onuffer (TRENDS in Pharm. Sci.) in Table page 460 reports MS, arthritis, sarcoidosis, allograph rejection, and cancer treatment as "possible therapeutic indications". Thus, such treatments were speculative and not established in 2002. Table 2 and Table 3, pages 462 and 463 confirm that no CXCR3 antagonists were in clinical development in 2002. The only complete paragraph in column 2, page 462 reports that CXCR3 was the subject of drug development programs. Thus, in 2002 CXCR3 antagonists were still in the experimental stage and any claims of

disease therapy are speculative in nature for which Applicants have provided no empirical support.

Proudfoot (Sem. Immun.) reports in the diagram on the top of page 59 that allograph rejection is the only "target" of CXCR3 ligand research. The first complete paragraph on page 61 states that inhibitors of only two the fifty chemokine receptors had progressed to clinical trials. Neither of these receptors was CXCR3. The last sentence in the paragraph states "[chemokines] have certainly been a difficult family to work with". Thus, in 2003, two years after Applicants filing date, only potential targets were art recognized and no therapeutic applications had been identified.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 136 as well as the hundred of diseases embraced by the term CXCR3 related disease. Thus, the scope of claims is very broad.

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP §2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry. Thus, undue experimentation will be required to determine if any particular claimed compound is, in fact, a treatment of any disease.

Applicants assert that they are enabled for treating allograph rejection, COPD, arthritis, and EAE. They also conclude that consideration of all factors discussed above leads to a conclusion of enablement, not of undue experimentation as asserted by the Examiner. This is not persuasive. Applicants can point to no reference teaching clinical efficacy for treatment of allograph rejection, COPD, arthritis, and EASE (which is not a disease) with any CXCR3 antagonist. The Examiner would welcome such evidence.

a) Applicants agree with the Examiner that the degree of experimentation required is huge. They point to the team of medicinal chemists, pharmacologists, pharmacists, and clinicians required to discover which of Applicants compounds are able to treat which diseases. They conclude that the experimentation is routine

but do not argue as to the amount required. Applicants are instructed to look at page 31 of Judge Larimer's opinion in University of Rochester v G.D. Searle from the District Court from the Western District of New York. This can be found at http://www.nywd.uscourts.gov/decision/20030305_00cv6161_larimer.pdf. The screening of 600 existing compounds over an eight-month period was given as an example of undue experimentation. Can one imagine what Judge Larimer' would have thought of the amount of experimentation required to synthesize Applicants' millions of compounds, screen them, and then test the active ones clinically against hundreds of diseases?

b) The Applicants correctly to point to the passage spanning line 29, page 21 to line 23, page 24 as giving direction for preparing formulations. The Examiner in the previous office action erroneously omitted this. Applicants assert that the physician determining the doses of Applicants' compounds could use doses employed for antagonists of chemokine receptors other than CXCR3. Applicants do not dispute that no CXCR3 antagonist has even been used in the clinic. Since there are dozen of chemokine receptors with differing substrate specificities, binding affinities, and agonist/antagonist properties, Applicants assertion that unrelated molecules could be used to determine doses is not logical. Do Applicants' molecules bind to all known chemokine receptors equally? Which

specific known chemokine antagonist is Applicants going to use? Does this unrelated chemokine antagonist even bind to CXCR3? Applicants assert but offer no evidence showing correlation between their screens and clinical efficacy. The Examiner offered scientific reasoning as to why no such correlation could be known.

c) Applicants agree there are no working examples of disease treatment in the specification. d) Applicants dispute that the invention concerns clinical treatment of human disease with antagonists of the CXCR3 receptor. They do not say what it does concern. In the discussion of the practitioners of the invention, Applicants listing of medicinal chemists, pharmacologists, pharmacists, and clinicians suggests that the claims are drawn to discovery of uses of the compounds. The plain meaning of "treating", used in the claim, has nothing to do with discovering. e) Applicants dispute the state of the art of clinical usage of CXCR3 antagonists. They point to six research articles as support of such clinical use. None of these articles concerns any human or animal treatment of any disease. None has any clinical data for any CXCR3 antagonist. The nasty fact remains that as of today no CXCR3 antagonist has even been used in the clinic for the treatment of any disease. As of Applicants filing date in 2001, no such use was art-recognized by physicians.

f) Applicants dispute the identity of the practitioners of these claims and of the skill in the art. As discussed above, "treating" can only be done by a physician. No chemist or pharmacologist has the ability to treat anyone. The Examiner agrees that whoever the practitioners are, they are highly educated and experienced. However, no matter how highly trained, the skill in the art of clinical usage of CXCR3 antagonists is low, since no one has yet accomplished that feat. g) Applicants dispute the predictability in these arts. They assert the clinical arts are predicable but offer no evidence. The case law cited by the Examiners says that clinical arts are inherently not predictable. In this case, lack of clinical efficacy of any CXCR3 antagonists means that predictability is non-existent. h) Applicants dispute the wide breadth of the claims. They assert that the common core of formula 1 somehow means that millions of compounds are not included by the formula. Exactly how many compounds do they think formula I embraces? Applicants assert that the scope of diseases to be treated is small. Since they will not even list the diseases to be treated, assert that some infections but not other are covered, and argue that patients will differ as if any specific infection is CXCR3 related or not, how many different diseases do they think these claims cover?

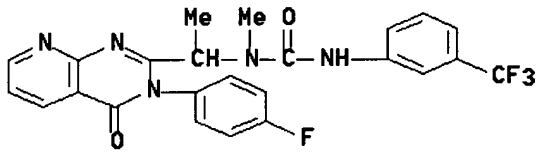
Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197, and 202 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Baxter ('005). The reference teaches the compound with registry number 330796-36-6 shown below. The Applicants claim the compounds with n = 0, X = C(O), R^{14} = 4-fluorophenyl, R^1 = methyl, R^2 = hydrogen, and Q = C(O). The reference teaches such a compound with L-R^3 = methyl and R^4 = 3-(trifluoromethyl)phenyl-NH-. Applicants claim the compounds with L-R^3 = alkylene-heteroaryl and R^4 = 3-(trifluoromethyl)phenyl. The compound is shown in the reference in lines 18-35, column 80. It is pictured in column 77 and is compound (20). The difference between the claimed and taught compounds is the urea rather than amide linkage to R^4 and the methyl group rather than alkylene-heteroaryl as L-R^3. These deficiencies are taught internally in the reference. Lines 30-31, column 32 teach that Applicants' claimed N-C(O)- linkage can replace urea linkage found in the

working example (20). Alkylene-heteroaryl is taught as one of four possible substituents that would make up the R^8 radical in the reference in lines 50-56, column 30. This R^8 radical corresponds to Applicants L-R^3 radical.



Lines 1-6, column 52 of the reference teach that cancer treatment is an intended use of the compound shown above. Thus, the intended utility is the same as Applicants' and claims 162, 163, 165, 166, 168, 169, 173, 174, 177, 179, 181, 183, and 184 are made obvious. Formulations are taught in lines 7-54, column 52. Thus, claim 153 is made obvious. Treatment of psoriasis is taught in lines 1-15, column 51 of the reference. Thus, claims 154, 155, 158, 187, 188, 195, and 202 are made obvious. Use of the compound discussed above for artificial and embryonic liver transplants is taught in lines 64-67, column 42 of the reference. Thus, claims 193, 194, and 197 are made obvious. The reference is silent as to the ability of the obvious compounds to antagonize CXCR3. However, the discovery of the mechanism of action of an obvious use or the mechanism of action of an obvious compound does not make that use or those compounds patentable. Thus, claims 156, 157, 170, and 190 are made obvious.

Applicants make three arguments concerning this rejection. Firstly they assert that Baxter ('005) is not enabling for making Applicants' claimed amide compound. Secondly, they assert there is no motivation for making the changes required to change the taught compound into the claimed compound and the Examiner used hindsight reasoning to make those two changes. Thirdly, they assert that one must choose between too many variables to assemble Applicants' claimed compound from the Markush lists found in the reference. This is not persuasive.

Firstly, Baxter ('005) teaches making his urea by reaction of an amine with m-trifluoromethyl isocyanate. Replace by m-trifloromethyl benzoyl chloride for the isocyanate will allow for synthesis of Applicants' claimed compound from the same amine. This is well within the ability of the average organic chemist. Secondly, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392,

170 USPQ 209 (CCPA 1971). The direction was found internally in the reference to make the required changes as discussed in the previous office action.

Thirdly, the amide linage was selected from a list of three possible linkages. The alkylene-heteroaryl is taught as one of four possible substituents. Even together this represents only twelve possible combinations. The medicinal chemist seeking to improve the potency and efficacy of his compounds can easily explore these.

8. Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197, and 202 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baxter (WO 01/19800 A2, Ref AL). The compound taught by this reference was discussed above. It is found in lines 21-29, page 108. Claims 31-39 of the reference are drawn to the compound above and claim 37 provides the direction to replace the taught urea linkage with an amide linkage. Lines 5-8, page 123, claim 31 provide the teaching that alkylene-heteroaryl is one of four possible substituents that would make up the R^8 radical in the reference. Compositions are taught in claims 29 and 30 of the reference. Claims 1-28 of the reference are drawn to inhibiting altered growth states of cells and the meaning this teaching was discussed above as was Applicants response.

Allowable Subject Matter

9. Claims 140, 141, 144, 146, 148, 150-152, 202, and 203 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

10. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK